REMARKS

Status of the claims

Claims 1-10 are pending. Claim 1 has been amended to conform to the Examiner's suggestion; no new matter has been introduced. Entry of the amendment and reconsideration of the claims in view of the following comments is respectfully requested. With respect to the amendment, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Discussion of Rejection Under 35 U.S.C. § 112, second paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claim language is definite when the metes and bounds of the invention can be adequately determined. *In re Goffe,* 526 F.2d 1393, 1397 (CCPA 1975). The Examiner alleged that the recitation of the phrase "an elevated blood pressure" is vague and indefinite because there is no point of reference with which to determine if a blood pressure would be considered elevated. The Examiner further suggested substituting the phrase "hypertension" for "an elevated blood pressure" to eliminate the ambiguity. Applicants have amended claim 1 to be in conformance with the Examiner's suggestion in order to advance prosecution. Accordingly, the present rejection is now moot and should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 102

The Examiner has rejected Claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Hariawala et al. (*J. Surg. Res.* 63: 77-82, 1996). Applicants respectfully traverse this rejection.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be

no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed. Cir. 1991).

Hariawala et al. teach that intracoronary (IC) administration of 500 μg of VEGF to normal nonischemic pigs resulted in severe hypotension within 4 minutes of drug administration. (p. 80). The hypotension was so severe that, when a similar IC administration of VEGF was carried out in the porcine model of chronic myocardial ischemia, half of the VEGF-treated animals died. (pp. 78-79). The Examiner speculated that the pigs used in the cited reference could reasonably be expected to have 'an elevated blood pressure' because animals which are under research conditions frequently have a blood pressure above what would be found in an animal in its natural environment. (p. 4 of the OA). However, the speculation of the Examiner is not part of the reference and nothing therein discloses that any of the pigs had an elevated blood pressure. In fact, prior to the injection of VEGF, the animals were thoroughly anesthetized which would be expected to result in lower, not higher, blood pressure. This outcome is illustrated in Fig. 5 of the reference, which depicts the pigs' mean arterial pressure dropping from 85 mmHg to less than 40 mmHg, which suggests that the pigs were within the normal range of blood pressure before the administration of VEGF. (p. 80).

Thus, since Hariawala et al. do not disclose the administration of VEGF to a patient with an elevated blood pressure (or hypertension, for that matter), the strict identity standard of anticipation under 35 U.S.C. § 102 is not satisfied. Accordingly, Applicants respectfully request that this anticipation rejection be withdrawn, and the pending application allowed.

Discussion of Rejections Under 35 U.S.C. § 103

Guyton in View of Roberts et al.

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Guyton (*Textbook of Medical Physiology*, 8th ed., W.B. Saunders Co., pp. 209-18, 1991) in view of Roberts et al. (*J. Cell Sci.* 108: 2369-79, 1995).

The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Third, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

The Examiner argued that it would have been *prima facie* obvious to treat an individual with hypertension with VEGF because Guyton teaches that individuals with essential hypertension have an impaired ability to excrete salt and water and because Roberts et al. teach that VEGF functions to increase the permeability of endothelium and that the kidney glomeruli have fenestrated endothelium, which are more permeable to small solutes. Applicants respectfully traverse this rejection because one of ordinary skill in the art would not have been motivated to combine these references to achieve the claimed invention.

Guyton teaches that, in addition to the failure to excrete adequate amounts of salt and water in the absence of a high arterial pressure, patients with essential hypertension have decreased renal blood flow and increased resistance to blood flow through the kidneys. (p. 217). Despite the great increase in real blood flow, the glomerular filtration rate is often very near normal. The reason for this is that the high arterial pressure still causes adequate filtration of fluid though the glomeruli into the renal tubules. (*Id.*, emphasis added). Guyton further teaches that the exact reason for the failure of the kidneys of essential hypertensive persons to excrete salt and water at normal blood pressure levels is unknown. (*Id.*) However, "the very significant vascular changes in the kidneys… suggest that decreased renal blood flow is the cause of this." (*Id.*, emphasis added).

Roberts et al. teach that VEGF induces the formation of endothelial fenestrations. (p. 2374). Since the kidney glomeruli have fenestrated endothelium, the induction of additional fenestrae may positively affect the glomerular filtration rate. However, nothing in Roberts et al. teaches or even suggests that VEGF is capable of increasing the renal blood flow, which is identified by Guyton as a probable cause of the hypertension. Therefore, since Guyton teaches that the glomerular filtration rate in essential hypertensive patients is near normal, and that the likely cause of their inability to excrete adequate amounts of salt and water under the normal arterial pressure is the decreased renal blood flow, the teaching of Roberts et al. that VEGF induces the formation of endothelial fenestrations does not provide a motivation to combine the references or a reasonable expectation that administration of VEGF would promote the excretion of salt and water in essential hypertensive patients. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, and therefore this objection under 35 U.S.C. § 103(a) should be withdrawn.

Guyton in View of Hariawala et al. Further in View of Zioncheck et al.

Claims 1 and 5-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Guyton (*Textbook of Medical Physiology*, 8th ed., W.B. Saunders Co., pp. 209-18, 1991) in view of Hariawala et al. (*J. Surg. Res.* 63: 77-82, 1996) further in view of Zioncheck et al. (U.S. Pat. No. 6,485,942). The Examiner alleged that it would have been *prima facie* obvious to treat with hypertension with VEGF, including VEGF121 or VEGF molecules with an altered heparin binding domain to decrease blood pressure in view of the teachings og Guyton discussed above and because Hariawala et al. teach that VEGF administration causes vasodilation which decreases blood pressure and because Zioncheck et al. teach that these forms of VEGF either do not bind heparin or bind it at a lower affinity, resulting in a VEGF which has a slower rate of clearance from the body. For the reasons stated below, Applicants respectfully traverse this rejection.

First, as discussed above, Hariawala et al does not teach administration of VEGF to patients with high blood pressure. Second, intracoronary administration of VEGF to healthy and ischemic pigs was accompanied by rapid and severe hypotension, with an average drop in mean arterial blood pressure in healthy animals of about 44% and a significant rate of mortality in ischemic animals. (p. 80). Hariawala et al. teach that the "severe hypotension which accompanied intracoronary VEGF administration at the dosage level utilized in this study… would obviously present a significant

clinical problem" and that "prior to any clinical evaluation of VEGF, the problems related to its hypotensive effects would have to be dealt with." (p. 81, emphasis added). Hariawala et al. even suggest using gene therapy to allow delivery of smaller amounts of VEGF over a longer period of time, avoiding the hypotensive effects of bolus injection.

A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness... MPEP 2145 X.D.1 at 2100-169 (quoting *In re Gurley*, 27 F.3d 552, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)). It is improper to combine references where the references teach away from their combination. MPEP 2145 X.D.2 at 2100-169 (quoting *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)). Since Hariawala et al. viewed the severe hypotension associated with the administration of VEGF as a "significant clinical problem" to overcome, the reference actually teaches away from using VEGF to treat anything except coronary insufficiency. Therefore, it was improper to combine it with Guyton under MPEP 2145 X.D.2.

Zioncheck et al. teaches that C-terminal truncations of VEGF result in peptides with slower rates of clearance and lower volumes of distribution. (col. 2, lines 44-46). Zioncheck et al. do not teach administration of VEGF to hypertensive patients, or a method to overcome the severe hypotensive effect of VEGF reported by Hariawala et al. Thus, Zioncheck et al. do not teach anything that would cure the deficiencies of Hariawala et al. in terms of its failure to provide a suggestion or motivation to combine, or a reasonable expectation of success from combining, with Guyton. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, and therefore this objection under 35 U.S.C. § 103(a) should be withdrawn.

Guyton in View of Hariawala et al. Further in View of Cid et al.

Claims 1-10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Guyton (*Textbook of Medical Physiology*, 8th ed., W.B. Saunders Co., pp. 209-18, 1991) in view of Hariawala et al. (*J. Surg. Res.* 63: 77-82, 1996) further in view of Cid et al. (U.S. Pat. No. 5,318,957). The Examiner argued that it would have been *prima facie* obvious to treat individuals experiencing hypertension with VEGF in order to increase the excretion of salt and water in said individuals in view of the teachings of Guyton and Hariawala et al. discussed above and further in

view of Cid et al., because Cid et al. teach that angiogenic factors are useful for treatment of conditions which involve angiogenesis and because Guyton teaches that that hypertension can cause a number of conditions which involve angiogenesis. For the reasons stated below, Applicants respectfully traverse this rejection.

First, all of the above arguments relating to the problems with Hariawala et al. apply with equal force here. Hariawala et al. do not teach the administration of VEGF to patients with hypertension, and they actually teach away from using VEGF for treatment of any diseases except cardiac ischemia due to its severe hypotensive effect. Thus, Hariawala et al. cannot be properly combined with Guyton.

Just like Zioncheck et al., Cid et al. fail to correct the deficiencies in Hariawala et al. Cid et al. teach that some angiogenic factors may be useful for treatment and prevention of diseases involving angiogenesis such as myocardial and cerebral infarctions, mesenteric or limb ischemia, wounds, and vascular occlusion or stenosis. (col. 1, lines 63-68). Cid et al. do not teach that VEGF may be useful for treatment and prevention of diseases involving angiogenesis, or that *any* angiogenic factors may be useful for treatment and prevention of hypertension. Guyton teaches that hypertension sometimes leads to congestive or coronary heart disease, stroke, or kidney failure (p. 209) – all conditions that, according to the Examiner, *involve* angiogenesis (emphasis added).

Just because hypertension sometimes *leads* to heart failure, stroke, or kidney failure, does not imply that any treatment for heart failure, stroke, or kidney failure would be obviously useful for treating hypertension. Myocardial and cerebral infarctions, ischemia and stenosis are all conditions in which critically important tissues – heart muscle, brain, etc. – become necrotic due to lack of oxygenation. Thus, any drug which promotes rapid delivery of oxygen to the affected tissues, including angiogenic factors, may be useful for treating these acute indications. Hypertension, on the other hand, is a chronic condition which has little if anything to do with oxygenation. Therefore, the reasoning behind the use of angiogenic factors for treatment and prevention of diseases involving angiogenesis in Cid et al. is simply not applicable to the use of VEGF for treatment and prevention of hypertension. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, and therefore Applicants respectfully request that this objection be withdrawn.

Discussion of Rejection for Obviousness-Like Double Patenting

Claims 1-10 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 of copending U.S. Application No. 10/749,706, because – although the claims are not identical – they are not patentably distinct from each other because they are both directed to treatment of hypertension by the administration of VEGF (see p. 10 of the OA). Applicants request to hold this issue in abeyance until such time the claims of either application are held allowable.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 219002030901. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By /James J. Mullen, III/
James J. Mullen III, Ph.D.
Registration No.: 44,957
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-7940